MEMORANDUM

Clinical Review of MTI, Onyx® Liquid Embolization System

DATE: July 8, 2003

SUMMARY: This original PMA is for the Onyx® Liquid Embolization System.

Indications for Use

The Onyx® Liquid Embolization System is an artificial embolization device intended for use in the treatment of brain arteriovenous malformations, when embolization is indicated to minimize blood loss to reduce the BAVM size prior to surgery.

Device Description

Onyx® Liquid Embolization System is intended for use by the interventional neuroradiologist when therapeutic or palliative embolization of a BAVM is indicated to minimize blood loss or to reduce the BAVM size prior to surgery or radiosurgery.

The liquid Onyx is a mixture of ethylene vinyl alcohol co-polymer (EVOH) dissolved in dimethyl sulfoxide (DMSO). Micronized tantalum powder is suspended in the liquid polymer/DMSO mixture to provide fluoroscopic visualization. The Onyx material is delivered in a liquid phase through a microcatheter to the target lesion under fluoroscopic control. Upon contact with blood (or body fluids) the solvent (DMSO) rapidly diffuses away causing in-situ precipitation of a soft radiopaque polymeric embolus.

Onyx is available in a range of liquid viscosities intended to have delivery and precipitation characteristics optimized for the type of lesion being treated. Lower viscosity Onyx formulations, achieved by reducing the polymer/DMSO ratio, are appropriate for embolization of AVMs where depth of penetration in small diameter vessels is required for effective embolization. These Onyx formulations, designated as Onyx-18 and Onyx-34, have a nominal liquid viscosity of 18 and 34 centistokes respectively. Onyx-34 is recommended when feeding pedicle injections will be conducted close to the nidus at flow rates up to 200 ml/min and in 3 mm or smaller diameter vessels. Onyx-18 will travel more distally and penetrate deeper into the nidus due to its lower viscosity; therefore, it is recommended when feeding pedicle injections will be conducted close to the nidus and the flow rate is lees than 50 ml/min. Final solidification occurs within 5 min for both product formulations. Coil placement prior to Onyx injection should be considered for feeding pedicles with AV fistulae having flow rates in excess of 200 ml/min and vessel diameters of 3 mm or greater.

The liquid Onyx is delivered through a DMSO primed micro catheter selectively placed within a feeding pedicle of an AVM at a slow rate of approximately 0.16 ml/min. Precipitation of the material begins immediately upon injection, beginning as a "skin" on the outside of the mass. Total precipitation occurs within minutes. The distance that Onyx travels before solidifying within the vasculature depends on a number of factors, including the flow rate in the vessel and the rate of injection. In AVM applications, embolization is intended to reduce the risk of rupture and subsequent stroke.

The MTI UltraFlow™ micro catheters are intravascular flow directed micro catheters intended for delivery of specified agents for diagnosing or treating vascular diseases of the distal and peripheral anatomy. The catheters are DMSO compatible single lumen end-hole catheters. The MTI Rebar™ micro catheters are designed for use in the neuro vasculature and for delivery of DMSO and Onyx after selective placement in the target lesion. The Rebar catheter is a single-lumen catheter designed to be introduced over a steerable guidewire.

Adjunctive device compatibility testing demonstrated that Onyx successfully solidified and occluded simulated vessels up to 5 mm with deployed coils and that DMSO did not leach any materials from the tested coils. Also, there was no chemical interaction shown with Onyx and histoacryl glue.

Alternative Procedures

Endovascular embolization of BAVMs involves the use of catheters to deliver various occlusive agents, such as permanent balloons, sclerosing drugs, thrombosing coils, PVA particles, and rapidly acting glues, such as n-Butyl cyanoacrylate.

Background

Onyx was initially used in clinical feasibility studies at UCLA, Mexico City, and various European countries. To date an estimated 1575 patients with AVMs have been treated with Onyx throughout Europe, Australia, Canada, and select Eastern and South American countries. *Please provide any available safety data on the estimated 1575 patients with AVMs have been treated with Onyx throughout Europe, Australia, Canada, and select Eastern and South American countries.*

Cerebral AVMs occur when there is an abnormal development between the arteries and veins. Normally blood flows from the arteries to the veins via a capillary bed, but capillary beds are missing in AVMs. AVMs develop as an abnormal tangle of vessels where the arteries are directly connected to the veins. Without the capillary bed, blood is allowed to flow from arteries to veins at high pressure. This high pressure through the veins causes them to dilate and may continue to hemorrhage.

AVMs are thought to develop during the early stages of life and generally do not become symptomatic for the patients until between 20 and 50 years of age. 3 out of every 10,000 persons are thought to have an AVM. About 50% of malformations present with intracranial hemorrhage and 25% with partial seizures and epilepsy. The remaining 25% present in the form of migraine headaches, focal or general neurological deficits and cranial nerve dysfunctions. The annual incidence of intracranial hemorrhage due to AVMs is between 1 and 3 per 100,000.

There are currently several treatments for AVMs including microsurgery, radiosurgery, and endovascular embolization in combination with micro or radiosurgery. Microsurgery uses bipolar cauterization and surgical clips to remove the arterial feeders and retain the transit artery. The advantages of microsurgery are: 1) the procedure can remove the total AVM abnormality during the procedure, 2) it has a proven track record, and 3) it can be used to treat small and large AVMs; the disadvantages are 1) it is invasive, requiring a craniotomy, 2) the patient is placed under general anesthesia for the surgical procedure, and 3) certain deep intracranial AVMs cannot be treated. Results discussed by Deruty demonstrated that for lesions of all sizes, a "favorable" outcome can be expected from microsurgical resection in 81% to 95% of patients; the mortality rate varies from 1 to 4%.

Radiosurgery involves an intense targeted radiation that induces endothelial damage, subendothelial deposition of collagen, and proliferation of vascular smooth muscle in vessels, leading to eventual obliteration of the malformation. The advantages of radiosurgery are that it does not require a craniotomy and it allows for treatment of some small deep lesions that can not be treated by microsurgery; the disadvantages are: 1) typically lesions larger than 2.5 cm are not treated effectively, 2) there is an increased possibility of hemorrhage post procedure, and 3) there exists a risk of injuring adjacent brain tissue. Total obliteration rates of AVMs have been reported to be greater than 80% with the gamma knife, particle beam, and linear accelerator techniques for lesions with a diameter under 1-3 cm.

Endovascular embolization involves the use of catheters to deliver a variety of occlusive agents such as permanent balloons, sclerosing agents, thrombosing coils, and rapidly acting glues. The advantages of embolization are: 1) no craniotomy is required, 2) can treat deep AVMs by treating small areas at a time and allowing the surrounding brain tissue to recover, and 3) the area to be treated can be tested to determine the reaction of the area prior to the permanent treatment; the disadvantages are: 1) they often require multiple treatments and 2) they are not effective in completely obliterating the malformation. Gobin has reported that embolization has little chance of completely occluding an AVM unless the lesion is small or has less than 3 feeding vessels. Embolization is useful when combined with microsurgery or radiosurgery. The most widely used embolization technique for AVMs is the injection of acrylic-based glues. Morbidity and mortality rates associated with embolization procedures were reported by Gobin as 13% and 2% respectively. Vinuela reported a cumulative rate of persistent deficits of 9% and a mortality rate of 4% for patients who underwent staged embolization procedures followed by surgical resection. The most widely used embolic agents for AVMs are the liquid acrylic-based glues. The difficulties with the glues are the lack of control in delivery and the adhesion to all surfaces, including the catheter.

DMSO is an organic solvent used in a variety of medical applications, including the treatment of intracranial hypertension, and as a bladder irrigant. DMSO is excreted unchanged in the urine or oxidized to dimethyl sulfone. Chaloupka reported on the potential angiotoxicity of DMSO and observed significant technical difficulties, vasospasm and angionecrosis is a swine endovascular emobolization model. Subsequent studies using Onyx and DMSO in a similar swine model, showed no significant vasotoxicity or vasospasm when these materials were injected in accordance with the method described in the labeling.

Clinical Study

Objective

Demonstrate that Onyx was no worse than n-BCA in terms of efficacy within a 20% specified clinical tolerance.

Design

The study was designed as a non-inferiority trial with the objective of demonstrating that Onyx is no worse than the Cordis TRUFILL n-BCA. Informed consent was obtained from 113 patients. 108 patients were randomized (57 n-BCA and 51 Onyx). Two of the patients randomized were late screen failures identified at the time of the initial embolization procedure prior to attempted treatment. During the diagnostic angiogram for one of the patients, 18-003, the physician discovered that the AVM was in a territory of the brain that was not suitable for embolization; the other patient, 21-009, underwent an angiogram for the procedure and the physician noted that the lesion had a very rapid filling rate of a very large venous matrix and did not continue with any embolization treatment. Patient 21-009 was subsequently treated with PVA particles and liquid coils over 3 staged embolizations; there were two adverse events, back pain and groin hematoma, both of which resolved prior to hospital discharge. Thus, 106 patients were enrolled in the study and randomized (55 n-BCA and 51 Onyx). 6 patients originally enrolled as AVM cases were subsequently reviewed by the core lab and determined to have dural ateriovenous fistulae, 1 n-BCA and 5 Onyx, (2-008, 5-005, 8-010, 8-014, 38-001, and 8-008). The core lab has categorized these patients as protocol violations and has recommended they be removed from the analysis since they have a different pathology. A total of 100 true BAVM patients had treatment attempted and were included in the ITT analysis, 54 n-BCA and 46 Onyx. Patients underwent embolization to reduce the size of the AVM prior to surgical resection. Neurological assessments, i.e. NIH scale, Barthel Index, and Glasgow Index, were performed prior to and post embolization and/or surgical resection, when surgery was performed. Patients without total resection were followed at 3 and 12 months. 86 patients had a total resection, 45 n-BCA and 41 Onyx. 9 have either had a partial resection, radiosurgery, or no surgery, 6 n-BCA and 3 Onyx; these patients will be followed for safety at 3 and 12 months post-procedure. *You state that 9 patients have either had a partial resection, radiosurgery, or no surgery, 6 n-BCA and 3 Onyx; these patients will be followed for safety at 3 and 12 months post-procedure. Please state the patient ID and the procedure they had and why total surgical resection was not possible. According to information in the PMA, it appears that 6 n-BCA and 3 Onyx patients had partial resections.* 3 patients are ongoing, 1 n-BCA and 2 Onyx. One of the ongoing patients, 3-003, received a single embolization with Onyx; the second embolization was a failure for Onyx delivery and the patient was crossed over to n-BCA; another embolization procedure is not yet scheduled. One of the other two patients, 38-004 had their latest embolization on Feb. 28, 2003 and is anticipated to go to surgery on March 13, 2003; the third patient will have the embolization on March 5, 2003. 2 n-BCA patients were lost to follow-up. One of the patients, 20-002 received 2 embolization treatments and was lost to follow-up; the other patient, 10-003 received one embolization treatment and withdrew from the study. A total of 98 patient, 52 n-BCA and 46 Onyx, were available for post-embolization treatment.

	N-BCA	Onyx
# Pts enrolled	55	51
Protocol violation	1	5
Dural fistulae patients		
Complete surgical resection	45	41
Partial resection	6	3
Pts ongoing	1	2
Pts lost to follow-up	2	0

Site #	Site Name	N-BCA	Onyx	Total	%
8	Watson	7	7	14	13.0%
6	Pryor	7	6	13	12.0%
2	Barnwell	6	6	12	11.1%
21	Purdy	5	4	9	8.3%
29	DeNardo	5	4	9	8.3%
38	Mericle	5	4	9	8.3%
5	Rasmussen	4	4	8	7.4%
10	Mawad	4	2	6	5.6%
3	Berenstein	3	3	6	5.6%
1	Duckwiler	2	2	4	3.7%
18	Rosenwasser	2	2	4	3.7%
34	Sanders	2	2	4	3.7%
20	Rodriguez-Mercado	1	2	3	2.8%
32	Malisch	1	2	3	2.8%
30	Marks	2	0	2	1.9%
19	Dion	1	0	1	0.9%
28	McDougall	0	1	1	0.9%
40	Fessler	0	0	0	0.0%
33	Solander	0	0	0	0.0%
17	Chaloupka	0	0	0	0.0%
	Total	57	51	108	100%

3 sites did not enroll any patients due to late timing of IRB approval.

Please provide the name of the sites involved in the study and explain why they are not numbered 1 through 20.

Patient enrollement, excluding patients with dural fistulae

Site #	Site Name	N-BCA	Onyx	Total	%
6	Pryor	7	6	13	12.7%
2	Barnwell	6	5	11	10.8%
8	Watson	7	4	11	10.8%
29	DeNardo	5	4	9	8.8%
21	Purdy	5	4	9	8.8%
38	Mericle	5	3	8	7.8%
5	Rasmussen	3	4	7	6.9%
10	Mawad	4	2	6	5.9%
3	Berenstein	3	3	6	5.9%
1	Duckwiler	2	2	4	3.9%
18	Rosenwasser	2	2	4	3.9%
34	Sanders	2	2	4	3.9%
20	Rodriguez-Mercado	1	2	3	2.9%
32	Malisch	1	2	3	2.9%
30	Marks	2	0	2	2.0%
19	Dion	1	0	1	1.0%
28	McDougall	0	1	1	1.0%
40	Fessler	0	0	0	0.0%
33	Solander	0	0	0	0.0%
17	Chaloupka	0	0	0	0.0%
	Total	56	46	102	100%

Patient Demographics by Group n=102

Demographics	N-BC n=56	Onyx N=46
Age (yrs)		
Mean +/- SD (n)	35.1 $\pm$ 14.3 (56)	40.3 $\pm$ 16.3 (46)
Median (range)	36.0 (10.0-66.0)	42.5 (7.0-72.0)
Gender		
Male	48.2% (27/56)	43.5% (20/46)
Female	51.7% (26/56)	56.5% (26/46)
BMI		
Mean +/- SD (n)	24.4 $\pm$ 4.6 (53)	28.1 $\pm$ 6.3 (39) $p<0.05$
Median (range)	23.6 (15.1-37.2)	27.4 (16.7-45.0)
Systolic Blood Pressure (mmHg)		
Mean +/- SD (n)	123 $\pm$ 14 (56)	126 $\pm$ 16 (46)
Median (range)	120 (80-171)	123 (98-167)
Diastolic Blood Pressure (mmHg)		
Mean +/- SD (n)	70 $\pm$ 10 (56)	71 $\pm$ 12 (46)
Median (range)	70 (50-90)	70 (48-98)

No statis tical differences were noted except for BMI which was slightly lower in the n-BCA group; fewer of the Onyx patients had data on height and weight, 39 of 46, which may explain the difference.

In general, the medical history showed no marked differences were noted between the Onyx and n-BCA groups except for a higher number of patients with aneurysms in the n-BCA group.

Medical History	N-BCA	Onyx
n=102	n=56	n=46
CAD	1.8% (1/56)	6.5% (3/46)
HTN	19.6% (11/56)	17.4% (8/46)
Diabetes	5.4% (3/56)	4.3% (2/46)
Neuro History		
Seizure	19.6% (11/56)	10.9% (5/46)
Stroke	0.0% (0/56)	2.2% (1/46)
Aneursym	*8.9% (5/56)	0.0% (0/46)
Other AVM	3.6% (2/56)	0.0% (0/46)
Intracranial Hemorrhage (>1 yr)	11% (6/56)	6.5% (3/46)
Neuro Interventions		
Surgery (Clipping)	5.4% (3/56)	0.0% (0/46)

*p<0.05

Presenting symptoms were hierarchically evaluated based on the worst presenting symptom, i.e. acute bleed, remote bleed, neurologic deficit, neurologic symptoms, or no clinical symptoms. Neurological deficit includes seizures, hemiparesis, visual disturbances, and difficulty speaking. Neurologic symptom includes headache/migraine, nausea/vomiting, and nystagmus.

Hierarchical Presenting Symptoms	N-BCA	Onyx
n=102	n=56	n=46
Acute Bleed (<30 days)	14.3% (8/56)	15.2% (7/46)
Remote Bleed (>30 days<1 year)	17.9% (10/56)	19.6% (9/46)
Neurologic Deficit	51.8% (29/56)	39.1% (18/46)
Neurologic Symptoms	14.3% (8/56)	19.6% (9/46)
None	1.8% (1/56)	6.5% (3/46)

Approximately 34% of the total patients presented with some type of intracranial hemorrhage, i.e. either acute or remote. The majority of the patients had some type of neurologic deficit.

Patient 1-004 had more than one AVM treated and therefore the table represents 103 AVMs in 102 randomized patients. One patient who was a late screen had missing information on AVM characteristics so this patient is missing from the table. The pre-embolization AVM size was determined by the core laboratory.

Pretreatment Assessment n=103 AVMs in 102 pts	N-BCA n=57 AVMs in 56 patients	Onyx n=46 AVMs in 46 patients
AVM Location		
Right	55.4% (31/56)	63.0% (29/46)
Left	41.1% (23/56)	34.8% (16/46)
Midline	3.6% (2/56)	2.2% (1/46)
AVM in eloquent area of brain	48.2% (27/56)	45.7% (21/46)
Venous Drainage		
Deep	8.9% (5/56)	15.2% (7/46)
Superficial	62.5% (35/56)	63.0% (29/46)
Both	28.6% (16/56)	21.7% (10/46)
Spetzler-Martin Grade		
I	25.0% (14/56)	10.9% (5/46)
II	25.0% (14/56)	43.5% (20/46)
III	30.4% (17/56)	26.1% (12/46)
IV	19.6% (11/56)	19.6% (9/46)
AVM Size (Core Lab, mm^3)		
Mean$\pm$SD	16.0$\pm$20.0	26.3$\pm$45.2
Median	8.1	13.6
Range	0.08-94.9	0.17-290.5

AVM size was slightly higher in the Onyx group but this difference was not statistically significant, p=0.17. Both groups had the majority of the patients treated with AVMs having a Spetzler-Martin grade of either II or III.

On page 3147, you state that one patient who was a late screen had missing information on AVM characteristics so this patient is missing from the AVM Characteristics table. However, data is provided on 102 patients, 56 treated with n-BCA and 46 treated with Onyx. Please clarify this apparent discrepancy.

Baseline neurological status was evaluated using the Glasgow Coma Score, Barthel Index, and NIH stroke scale. Patients with a GCS of 8 or less are considered to be in a coma. All 3 scales indicated that the majority of patients treated in the study did not have severe neurological deficits at baseline. The Onyx group had a slightly higher percentage of patients with worse scores at baseline on these neurologic scales, i.e. almost 40% of the Onyx patients and only about 25% of the n-BCA patients had an NIH stroke scale>0 on entry into the study; the difference was not statistically significant.

Pretreatment Assessment	N-BCA n=56	Onyx n=46
Glasgow Coma Score		
0-6	3.6% (2/55)	2.2% (1/46)
7-14	3.6% (2/55)	8.7% (4/46)
>14	92.7% (51/54)	89.1% (41/46)
Barthel Index (Total Score)		
0-25	3.7% (2/54)	8.7% (4/46)
26-75	1.9% (1/54)	4.3% (2/46)
76-100	94.4% (51/54)	87.0% (40/46)
NIH Stroke Scale (Total Score)		
0	75.5% (40/53)	60.9% (28/46)
1-4	18.9% (10/53)	30.4% (14/46)
5-10	5.7% (3/53)	2.2% (1/46)
>10	0.0% (0/53)	6.5% (3/46)

A poolability analysis was done to ensure that data across all sites could be combined for analysis.

Characteristic	Fisher's Exact	F
Gender	P=0.86	
Assignment Group	P=0.99	
AVM Location	P=0.55	
Eloquent Part of Brain	P=0.40	
Spetzler-Martin Grade (1/2 vs 3/4)	P=0.02	
Presence of Bleed	P=0.11	
Age		1.26 p=0.24
BMI		0.93 p=0.54
SBP		0.71 p=0.78
DBP		1.50 p=0.12
AVM Size		1.92 p=0.03

The only significant differences were for Spetzler-Martin Grade and AVM size. The sponsor argues that since the Spetzler-Martin Grade was not found predictive of the primary safety and efficacy endpoints in the trial, it should not preclude pooling the results by site. The AVM size at site 34 had a considerably larger median AVM than the other sites; this variability is consistent with BAVMs and thus is representative of the general population.

Since 2 of the randomized patients were considered late screen failures, these tables and all subsequent tables are based on the number of patients enrolled which is 100.

# Embolization Procedures	n-BCA n-54		Onyx n=46	
	# Pts	% Pts	# Pts	% Pts
1	34	63.0%	26	56.5%
2	9	16.7%	11	23.9%
3	7	13.0%	6	13.0%
4	2	3.7%	1	2.2%
5	2	3.7%	1	2.2%
6	0	0.0%	0	0.0%
7	0	0.0%	1	2.2%
Total # Pts	54	100%	46	100%
Total Procedures	91		82	
Avg # Procedures/Pt	1.7		1.8	
(min, max)	(1,5)		(1,7)	

A total of 173 embolizations were performed in 100 patients, i.e. 82 in 46 patients treated with Onyx and 91 in 54 patients treated with n-BCA. The majority of patients were able to be treated with one embolization procedure.

	n-BCA	Onyx
	n-54	n=46
# Procedures	83	72
# Injections	203	183
Avg # Injections/Procedure	2.5	2.5
Onyx Usage Details		
Microcatheter Use (202 catheters)		
FlowRider		22
Ultraflow		151
Rebar		17
MTI Unknown		12
Initial Catheter Position		
n=183 Injections		
Wedged		36
Unwedged		144
Missing		3
Onyx Formulation Used		
Onyx-18 Alone		55/72 (76%)
Onyx-34 Alone		9/72 (13%)
Onyx-18 and 34		8/72 (11%)
No Agent Delivered		10 Procedures
Mean Vol Injection		0.50 ml
Mean Duration Injection		5.44 min
DMSO Usage		
Mean vol DMSO Injected		0.27 ml
Mean DMSO Injection Time		90.9 sec
N-BCA Usage Details		
Oil:n-BCA Ratio		
Within Guidelines (3:1-1:2)	71%	
Higher Concentration Oil	23%	
Higher Concentration n-BCA	6%	
No Agent Delivered	8 Procedures	
Mean Vol n-BCA Delivered	0.38 ml	

Of the 82 procedures in the Onyx group, 72 had Onyx injected; of the 91 procedures in the n-BCA group, 83 had n-BCA injected. Patients did not receive injection of the embolic agent for various technical reasons such as failed access or physician decision to utilize an alternative treatment. There were about 2.5 injections of the embolic agent per procedure.

The clinical protocol allowed for adjunctive procedures to be performed.

	n-BCA n-54	Onyx n=46
# Procedures in which Coils were used as adjunct	23/91 (25.3%)	*8/82 (9.8%)
Reason for Coil Usage		
High Flow Fistula	20	4
Other	3	4
Type of Coils Used[+]		
GDC	2	4
Straight Fiber Coil	1	2
3D	0	1
Liquid Coils	20	4

*p=0.008

[+]Multiple types of coils were used for a single patient

In most cases, the reason given for use of adjunctive coils was the presence of a high flow fistula. In 3 n-BCA cases and 4 Onyx cases, the adjunctive devices were used for other reasons. In 1 n-BCA case and 1 Onyx case, coils were used to treat an aneurysm. In the remaining cases, coils were categorized by the investigator to be necessary for some other safety reason, as allowed by the clinical protocol.

Events are considered technical or procedural if they are not associated with clinical sequelae. All technical and procedural events reported by the site underwent review by a medical monitor to ensure that these events did not result in clinical sequelae. When technical or procedural events that were not documented on the CRFs were identified by the medical monitor, these events were adjudicated and entered into the adjudication database as either technical or procedural.

	N-BCA	Onyx
Technical Events	n=54	n=46
System-Related Agent		
Delayed polymerization	1	0
Fragmentation of Onyx	0	1
Delivery Catheter Removal Difficulty	0	2
Poor Penetration/Visualization	0	5
Premature Polymerization	1	0
Prolonged Polymerization Time	3	0
Small Amount of Onyx in Vein	0	1
System-Related Catheter		
Catheter Shaft Rupture	0	*1
Delivery Catheter Removal Difficulty	0	5
Failed Access	3	3
Treatment Related		
Failed Access	1	0
Disease Related		
Failed Access	1	0
Other		
High Flow Fistula	1	0
Total Technical Failures	11	18
Procedural Events		
Embolization of unintended vessel	2	0
Laboratory/Imaging Abnormalities	6	2
Vasospasm	4	1
Total Procedural Events	12	3
Technical and Procedural Events		
Total Technical and Procedural Events	23	21
Total # Pts with Technical/Procedural Events	31.5%	30.4%
#Events/#Pts	17/54	14/46

*Device malfunction

There were 7 reported incidences of delivery catheter removal difficulty recorded on the CRFs. In 2 cases, the catheter removal difficulty was felt to be related to the agent having precipitated around the tip of the catheter. In the other 5 cases, it was attributed to the catheter itself; this may be related to different performance characteristics of the catheters required for Onyx administration as opposed to those used for standard embolization techniques. There were no clinical events related to these reported difficulties.

In one patient, 06-010, breakup of the embolic material occurred during injection into an undetected high flow component of the AVM. There were 8 reports of laboratory or imaging abnormalities; 4 (3 n-BCA and 1 Onyx) had silent infarctions in the distribution of the AVM on post embolization CT or MRI and 2 (1 n-BCA and 1 Onyx) had small areas of hemorrhage following embolization.

In all cases of vasospasm, the spasm resolved spontaneously and did not impede completion of the procedure.

Two n-BCA patients had embolization of an unintended vessel. In one patient, 08-006, embolic material was found on a routine chest x-ray. Work-up demonstrated a small, sub-segmental occlusion consistent with embolic material having transited the AVM to the venous system and having become lodged in a small pulmonary artery. In the second patient, 08-012, the site reported a prolonged polymerization time and subsequent small amount of embolic material in the draining vein.

Two events which occurred in the Onyx patients were considered device malfunctions, both catheter rupture, and the catheters were returned to MTI for analysis. In the first patient, 38-006, there was slight difficulty with delivery catheter removal following angiographic assessment at the close of the procedure; a Micro Therapeutics UltraFlow HPC flow directed micro catheter was used and gentle traction applied on a second attempt at catheter removal resulted in catheter release, there were no clinical sequelae. The catheter was returned for engineering analysis because the catheter shaft was noted to have ruptured during selective angiography utilizing a 1 cc syringe and

normal pressure; the analysis concluded that the catheter was built to specification and experienced a high pressure burst resulting from tube constriction (kink/prolapse) during use. In the second patient, 20-003, the site reported that a catheter shaft rupture of a Micro Therapeutics FlowRider Plus micro catheter, resulted in leakage of Onyx into the anterior and middle cerebral arteries with worsening seizures and neurologic changes; the event was categorized as a severe worsening neurologic status that was system related; the neurologic sequelae resolved by discharge. This event was similar to an event in Europe that prompted an advisory notice, August 2001, to all sites that recommended a modified technique for Onyx delivery, including recommendations to stop injection if resistance is felt or Onyx is not visualized exiting the catheter tip. The FlowRider Plus catheter is no longer a marketed product and has been replaced by an optimized UltraFlow catheter. The engineering report notes catheter rupture approximately 10 cm from the tip which is consistent with a very slow infusion rate imposed on a distal occlusion; there is a possibility that a slug of Onyx precipitated and became lodged in the catheter resulting in high pressurization and catheter burst just proximal.

A total of 89 patients had an attempt at surgical resection; 86 had a total resection, 45 n-BCA and 41 Onyx. Three patients had a partial resection and are being followed for safety at 3 and 12 months post-procedure. In general, patients required one surgical procedure to obtain total resection; a total of 98 surgical procedures were required to treat 89 patients; 7 patients, 5 n-BCA and 2 Onyx, required multiple staged procedures. The maximum number of surgical treatments attempted was 4 in one n-BCA patient, 29-003, resulting in complete surgical resection of the AVM. One n-BCA patient, 29-001, required a staged course of embolization and surgery based on physician assessment of the pathology; the patient had surgery after the first series of embolization procedures; another series of embolization procedures with a second surgical resection was then performed. The patient had successful embolization of the AVM and total resection after the second surgery.

On page 3153, in the Technical and Procedural Events table, 5 Onyx patients had poor penetration/visualization. Please specify which patients had poor penetration and which ones had poor visualization and discuss these events in detail.

Assessments

Baseline neurological examination and grading scales, including NIHSS, Barthel Index, and GCS, CT, MRI, and/or angiograms

After embolization, the patients were evaluated with the same scales except the Glasgow Outcome Scale Post Procedure was used.

Endpoint

Primary: 50% or greater angiographic reduction in AVM size by core laboratory was required for success.

Secondary:

- Surgical blood loss
- Surgical resection time

NIH Score Change from Baseline	Status	Change Post-Embolization N-BCA n=49	Onyx n=43	Change Post-Surgery N-BCA n=38	Onyx n=39
>0	Declined	10.2% (5/49)	11.6% (5/43)	36.8% (14/38)	28.2% (11/39)
0	Unchanged	71.4% (35/49)	72.1% (31/43)	52.6% (20/38)	59.0% (23/39)
1-5	Improved	18.3% (9/49)	14.0% (6/43)	10.5% (4/38)	10.3% (4/39)
>5	Improved	0% (0/49)	2.3% (1/43)	0% (0/38)	2.6% (1/39)

Barthel Score Change from Baseline	Status	Change Post-Embolization N-BCA n=50	Onyx n=43	Change Post-Surgery N-BCA n=40	Onyx n=38
1-10	Improved	2% (1/50)	0% (0/43)	5.0% (2/40)	0% (0/38)
0	Unchanged	68.0% (34/50)	72.1% (31/43)	50.0% (20/40)	52.6% (20/38)
5-10	Declined	12.0% (6/50)	4.7% (2/43)	5.0% (2/40)	7.9% (3/38)
15-50	Declined	12.0% (6/50)	16.3% (7/43)	12.5% (5/40)	15.8% (6/38)
51-100	Declined	6.0% (3/50)	7.0% (3/43)	27.5% (11/40)	23.7% (9/38)

Some patients did show a decline in their neurologic assessment but the percentage of patients was similar in both groups. This is likely due to a temporal correlation between the time of the intervention, embolization or surgery, and the time the neurologic assessments were made. For example, in many cases a Barthel Index was either unassessable or declined because the patient was prescribed strict bed rest post procedure and therefore the indices associated with ambulation were scored as a decline by default or the evaluation was not performed.

The Glasgow Outcome Scale is stratified based on the patients presenting Glasgow Coma Scale at baseline. Patients were categorized with either no deficit as baseline, Glasgow Coma Scale=15, or patients presenting with some level of deficit, Glasgow Coma Scale<15. Six of the patients with a Glasgow Outcome Scale reported post-embolization and/or post-surgery had a presenting Glasgow Coma Scale that categorized them as having some neurologic deficit, 3 n-BCA and 3 Onyx. All other patients had a normal Glasgow Coma Scale at baseline.

Presenting with normal Glasgow Coma Scale (=15)

GOS	Post-Embolization N-BCA n=46	Onyx n=40	Post-Surgery N-BCA n=36	Onyx n=34
0	80.4% (37/46)	67.5% (27/40)	66.7% (24/36)	47.1% (16/34)
I	17.4% (8/46)	22.5% (9/40)	11.1% (4/36)	23.5% (8/34)
II	0% (0/46)	7.5% (3/40)	5.5% (2/36)	17.6% (6/34)
III	2.2% (1/46)	2.5% (1/40)	11.1% (4/36)	11.8% (4/34)
IV	0% (0/46)	0% (0/40)	2.8% (24/36)	0% (0/34)
V	0% (0/46)	0% (0/40)	0% (0/36)	0% (0/34)

Presenting with Glasgow Coma Scale with Some Deficits (<15)

GOS	Post-Embolization N-BCA n=3	Onyx n=3	Post-Surgery N-BCA n=3	Onyx n=3
0	0% (0/3)	0% (0/3)	0% (0/3)	0% (0/3)
I	33.3% (1/3)	33.3% (1/3)	33.3 (1/3)	33.3% (1/3)
II	0% (0/3)	0% (0/3)	0% (0/3)	0% (0/3)
III	66.7% (2/3)	66.7% (2/3)	66.7% (2/3)	66.7% (2/3)
IV	0% (0/3)	0% (0/3)	0% (0/3)	0% (0/3)
V	0% (0/3)	0% (0/3)	0% (0/3)	0% (0/3)

One patient, 29-004, treated with Onyx, declined from baseline; all other patients remained the same.

The Glasgow Outcome Scale did not show any difference between the two groups either post-final embolization or post-surgery.

Please discuss the patients in the Glasgow Outcome Scale table on page 3158, since a higher percentage of Onyx treated patients had a score of I or II post-embolization and post-surgery.

Primary Efficacy Endpoint Analysis

An independent angiographic core lab read all angiograms at baseline and after the completion of all embolization procedures. The reader was masked to the treatment allocation and calculated the volume of the AVM obliteration based on a standardized method. The films were digitized using an automated system and stored on electronic media. The independent reviewer identified the margins of the AVM and digitized these points. The automated software algorithm was used to calculate the volume of the AVM and this information was stored on electronic media for each patient's AVM. In some cases, the automated system was not viable for technical reasons such as poor film quality or inconsistent views between baseline and post-embolization. In these cases, the core lab evaluated the volume of obliteration of the AVM using visual estimation against the dichotomous endpoint of >50% AVM exclusion.

Angiograms will include one AP and one lateral view, early, middle, and late phases for each of the three circulations, posterior, right anterior and left anterior. Adjunctive coil use was permitted/recommended for complete blockage of a large artery after embolization more distally with the liquid embolic agent; to block off arterial feeder which could not be safely embolized with the liquid embolic agent; to protect a normal arterial branch off a main artery from distal embolization with the liquid embolic agent; for flow arrest/reduction if angiography shows a high flow situation defined as the simultaneous appearance on angiography of venous drainage with arterial opacification,; to prevent trans-nidus passage of the liquid embolic agent into the venous side; or for other safety reasons determined by the investigator.

Percentage of Patients with ≥50% Exclusion of AVM

Intention-to-Treat	N-BCA	Onyx	Difference [95% C.I.]	Relative Risk
Primary Efficacy by Core Lab	84.3% (43/51)	97.6% (41/42)	13.3% [2.3%, 24.3%]	1.16 [1.01, 1.32]
Conservative Estimate with Ongoing Pts	84.6% (44/52)	93.2% (41/44)	8.6% [-3.8%, 20.9%]	1.10 [0.96, 1.27]
Per-Protocol				
Primary Efficacy by Core Lab	85.7% (42/49)	95.4% (41/43)	9.6% [-2.0%, 21.3%]	1.16 [0.97, 1.27]
Conservative Estimate with Ongoing Pts	86.0% (43/50)	93.2% (41/44)	7.2% [-5.0%, 19.4%]	1.08 [0.94, 1.24]

Diff=Onyx-n-BCA
RR=Onyx/n-BCA

Intention-to Treat Population

Two patients in the n-BCA group had films that were not analyzable based on the core lab assessment; the films were not in compliance with the protocol in that inconsistent views, required for assessment pre- and post-embolization were not submitted to the sponsor. These patients were removed from the analysis and categorized as protocol violations. One patient in the n-BCA group is still receiving embolization treatments and therefore has been removed from the analysis until embolization treatment is completed. A total of 51 patients were therefore available for the efficacy analysis in the n-BCA group.

Two patients in the Onyx group had films that were not analyzable on the core lab assessment; the films provided to the core lab did not contain the required consistent views from pre- to post-embolization. These patients were considered protocol deviations and have been removed from the efficacy cohort. In addition, two of the Onyx patients are still receiving embolization treatments and therefore cannot be assessed for efficacy yet. Therefore, a total of 42 patients are included in the efficacy analysis for the Onyx group.

	Total Pts=n	N-BCA=n	Onyx=n
Randomized	108	57	51
Late Screen Failures	2	2 (18-003, 21-009)	
Enrolled Pts	106	55	51
Protocol violations (Dural Fistulas)	6	1 (5-005)	5 (2-008, 8-001, 8-010, 8-014, 38-001)
Films not Analyzable	4	2 (21-008, 8-004)	2 (32-003, 2-001)
Pts Ongoing	3	1 (38-004)	2 (38-006, 3-003)
Total Accessible	94	51 Success n=43 *Failure n=8 Success Rate=84% (43/51)	42 Success n=41 *Failure n=1 Success Rate=98% (41/42)

*n-BCA Failures:

By core lab: 6-013, 19-001, 34-001, 2-012, 8-012, 8-007

Procedure failures: 8-006, 8-009

*Onyx Failures

By core lab: 6-007

Conservative Analysis

The conservative analysis takes into account the patients currently ongoing in the trial. Patients were assigned as a failure if they were randomized to Onyx and a success if randomized to n-BCA.

ITT Efficacy including Dural Fistula Patients

The n-BCA success rate remained at 84% and the Onyx success rate was reduced to 95%.

Predictors of Core Lab Success (n=100)

Characteristic	Core Lab ITT Failure n=9	Core Lab ITT Success n=84	p-value
Gender (%male)	44%	46%	P=1.00
AVM Location (%right/left)	89%	98%	P=0.27
Eloquent Part of Brain	22%	50%	P=0.16
Spetzler-Martin Grade (% 3 or 4)	22%	49%	P=0.17
Venous Drainage (% deep)	22%	39%	P=0.48
Presence of Bleed	44%	31%	P=0.46
Glasgow Coma Scale (<15)	11%	10%	P=1.00
Age (mean±sd, years)	39±13	37±15	P=0.71
BMI	34±4	25±6	P=0.29
SBP (mean±sd, mmHg)	130±22	123±14	P=0.36
DBP (mean±sd, mmHg)	75±6	70±12	P=0.27
AVM Size (median, mm^3)	8.7	11.6	P=0.95
# Embolization Procedures (mean±sd)	1.7±0.9	1.7±1.1	P=1.00
Randomization Group (% Onyx)	11%	49%	P=0.04

The only predictor of success by ITT is randomization group. Randomization to Onyx was associated with a higher success rate by ITT than n-BCA. Using a Fisher's Exact Test demonstrated a significantly better success rate for the Onyx group vs the n-BCA group (p=0.0377).

Please provide p-value for randomization group (% n-BCA).

On page 3163, in the Predictors of Core Labe Success (n=100) table, there are data for Core Lab ITT Failure (n=9) and Core Lab ITT Success (n-84) which is a total of 93 patients. Please explain this apparent inconsistency and recalculate the table based on the appropriate sample size.

Core Lab Measurements Quantitative Assessments

	N-BCA n=54	Onyx n=46
	With Quantitative Assessment	
% AVM Reduction post-embolization (mm^3)	n=37	n=23
Mean±SD	80±19	84±13
Median	85	83
Range	17-100	59-100
Frequency Distribution of % Reduction	% Pts With Quantitative Assessment	
0	0%	0%
10-24	2.7%	0%
25-49	5.4%	0%
50-74	24.3%	21.7%
75-99	54.0%	60.9%
100	13.5%	17.4%

The AVM size was larger in the Onyx group, although this difference did not reach statistical significance.

In the Cordis n-BCA randomized trial, mean percent reduction in AVM size was 79.4% for the n-BCA-treated group and 86.9% for the PVA control group.

Per-Protocol Analysis
A per-protocol analysis is defined as all patients in the intent to treat population that had at least one treatment with their assigned device; this group excludes any patient that is a primary technical failure since they did not receive any assigned embolic agent.

Primary Technical Failures: Four patients were technical failures during the first embolization procedure, 3 patients in the n-BCA group and 1 in the Onyx group. One patient in the n-BCA group, 19-001, could not be treated due to a high flow AVM that was not amenable to embolization with glue; the patient received PVA particles. The other two patients, 8-009 and 34-001, assigned to n-BCA did not receive any embolic agent because the physician could not access the AVM with the delivery catheter. The patient that was assigned to Onyx, 32-003, had a treatment attempt with Onyx but the physician was unsuccessful in reaching the target vessel with the delivery catheter; the patient was subsequently treated with n-BCA as standard of care. Thus 96 patients received the assigned embolic agent on their first attempt at treatment, 51 in the n-BCA group and 45 in the Onyx group and are included in a per-protocol analysis for efficacy. All the technical failure patients have been included in the intention-to-treat analysis and in the safety analysis.

One patient that was a primary technical failure with n-BCA, 34-001, went directly to surgery after the first embolization procedure and had a partial resection; this patient subsequently received another embolization treatment with n-BCA after this surgery. The patient is included in the ITT analysis and evaluated under the second series of embolization procedures, but was removed from the per-protocol analysis since they did not meet the criteria for inclusion. The patient films were reviewed by the core laboratory and the patient was classified as a treatment failure in the ITT analysis.

Two patients in the n-BCA group and 2 patients in the Onyx group were removed from the analysis because they had films that were unassessable or are still ongoing in the trial This results in a total of 49 patients in the n-BCA group and 43 patients in the Onyx group for the per-protocol analysis.

The per-protocol analysis defines a failure as either unsuccessful AVM angiographic exclusion as assessed by core laboratory or the inability to treat with the assigned agent for all staged embolization procedures. 3 patients in the n-BCA group were failures because they did not receive all embolizations with the assigned device. One Onyx patient, still receiving embolizations, is considered a failure in this per-protocol analysis since the investigator terminated treatment with Onyx and reverted to n-BCA during the second embolization procedure. The remaining failures, 4 n-BCA and 1 Onyx, were the result of incomplete exclusion of the AVM as assessed by the core lab.

Per-Protocol Analysis

	Total	N-BCA	Onyx
Randomized n	108	57	51
Late Screen Failures	2	2 (18-003, 21-009)	
Enrolled Pts	106	55	51
Protocol violations (Dural Fistulas)	6	1 (5-005)	5 (2-008, 8-001, 8-010, 8-014, 38-001)
ITT Analysis (Ever Attempted Treatment)	100	54	46
Technical Failures (During 1st attempt)	4	3 (8-009, 19-001, 34-001)	1 (32-003)
No embolization with Intended Device		51	45
Films not Analyzable	2	1 (8-004)	1 (2-001)
Pts Ongoing	2	1 (38-004)	1 (38-006)
Total Accessible	92	49 Success n=42 *Failure n=7 Success Rate=86% (42/49)	43 Success n=41 *Failure n=2 Success Rate=95% (41/43)

*n-BCA Failures:

By core lab: 6-013, 2-012, 8-012, 8-007

Procedure failures (Abandon treatment): 8-006, 21-007,21-008

*Onyx Failures

By core lab: 6-007

Procedure failure: 3-003

Please discuss the patients who are designated "late screen failures."

Blood loss during the surgical procedure was estimated based on the volume of blood lost in the suction canister and any other amount of blood loss from other sources that could be estimated from the site. In cases where a patient had more than one surgical procedure, an average value for each patient was calculated to provide an estimate of blood loss on a per patient basis.

	N-BCA	Onyx
Intention-to-Treat	n=44	n=43
Blood Loss Index*		
Mean±SD	892±1067	1127±1401
Median	475	550
Range	100-5000	50-6550

*p=0.55

No statistical differences were seen for estimated blood loss based on Spetzler-Martin Grade.

Data on surgical resection time for at least one surgical procedure was available for 42 patients in the Onyx group; 46 patients had surgical resection in the n-BCA group and surgical resection time was available for 42 of these patients. For those patients that had more than one surgical procedure, the average of all their surgical resection times was used for this per-patient analysis.

	N-BCA	Onyx
Intention-to-Treat	n=42	n=42
Surgical Resection Time (min)		
Mean±SD	411±201	399±179
Median	344	366
Range	150-1019	82-940

p=0.99

No statistically significant differences between the two groups were seen on surgery time by Spetzler-Martin Grade.

Safety

Adverse events were collected through hospital discharge for those patients that had a total surgical resection. For those patients, with either a partial resection or no surgery attempted, patient adverse events were summarized through 3 and 12 month follow-up.

The clinical trial had a DSMB that evaluated clinical events that were reported to MTI as serious or device related. In addition, all adverse events were reviewed by an independent medical monitor. This person is a physician independent of the clinical trial who reviewed all CRFs and source documents for all patients with reported AEs; this was performed by an independent consulting group, Boston Biomedical Associates. Once the adjudication of a patient's adverse events was completed by the medical monitor, a final review and approval was performed by the DSMB chairman. All serious or device-related adverse events, as adjudicated by the medical monitor or as reported by the sites, were reviewed. The DSMB chairman had the authority to override the adjudicator's assessment of the event if he deemed it necessary and appropriate.

Event	n-BCA n=54	Onyx N=46	Diff % [CI]	Relative Risk
Death	0 (0%)	2 (4.4%)	4.4% [-1.5, 10]	n/a
Intracranial Hemorrhage	8 (15%)	6 (13%)	-1.8% [-15, 12]	0.88 [0.33, 2.4]
Stroke	0 (0%)	1 (2%)	2% [-2.6]	n/a
Worsening Neuro Status	5 (9.3%)	7 (15%)	6% [-7, 19]	1.64 [0.56, 4.8]
Hydrocephalus	0 (0%)	2 (4.4%)	4.4% [-2, 10]	n/a
Seizures	0	1 (2%)	2% [-2,6]	n/a
Headache +/- nausea and vomiting	2 (3.7%)	0 (0%)	-3.7% [-9, 1.3]	0.0
Total patients	15 (27.8%)	19 (41.3%)	P=0.20	

Diff=Onyx-n-BCA RR=Onyx/n-BCA

In this table, only one event (worst event) is listed per patient. 15 patients in the n-BCA group and 19 patients in the Onyx group experienced at least one serious adverse event. There were no unanticipated adverse device effects.

The safety profile for the two groups is comparable. Although more patients in the Onyx group experienced a serious adverse event, the number of serious adverse events experienced was equal in the two groups, and there was not a statistically significant difference between the two groups for patient based serious AE rates. In addition, many of the events occurred during or post surgery.

Both deaths occurred following surgical resection. Patient 06-012, was a 52 year old woman with a right neck bruit which was found on a routine PE. Work-up revealed a frontal lobe AVM, Spetzler-Martin Grade II. She was asymptomatic and neurologically intact. On 10/9/02, she underwent embolization with multiple injections of Onyx which resulted in a 72% reduction of the AVM; except for headache and mild access femoral discomfort, the procedure was uncomplicated; she had no new neurological findings. On 10/11/02, the patient underwent elective surgical resection of the AVM; during the surgical procedure, the patient had extensive bleeding, EBL 5-6 L with transient hypotension. The bleeding source was difficult to control but ultimately adequate hemostasis was obtained

and the surgery was completed; she had an initially uncomplicated post-op course, including a post-op angiogram that documented total resection of the AVM. She was extubated, awake and responsive. That evening she experienced a severe headache, became less responsive, and required re-intubation; this was performed emergently on 10/11/02. At the time of this operation, a hematoma in the previous resection bed was evacuated and bleeding sites were coagulated. After lining the resection cavity with Surgicel, no further bleeding was seen and the procedure was completed. Following this reoperation, she was maintained in a barbituate coma. During her post-op course she had increasing intracranial pressure that required ventriculostomy placement on 10/17/02 for management. By CT, she also had persistent hematomas and ultimately significant infarction felt to be related to herniation through her craniotomy site. She was pressor dependent to maintain the barbituate coma and developed renal failure requiring CVVH. She demonstrated no improvement in neurologic function throughtout this period. Ultimately after discussion with the family, care was withdrawn and she expired on 10/19/02. Please clarify whether the radiopaque material that was found in the vein of Galen in patient 06-012, was Onyx. Please provide copies of angiograms for panel review.

The other patient, 08-005, was a 50 year old man who had a subarachnoid hemorrhage in October 1989, apparently related to an aneurysm that underwent surgical clipping. He had a stroke in May 2001, presenting with hemiparesis and at this time his AVM was diagnosed. The AVM was a large, high flow, predominantly dural based, Spetzler-Martin Grade III. He had a history of seizures and headaches. On enrollement into the study, he had a moderately severe hemianopia, an NIH Stroke score of 1 and a Barthel of 100. He was randomized to Onyx and had the initial embolization on 11/20/01. There were no technical difficulties but follow-up examination demonstrated slight worsening of the NIH Stroke scale to 3, due to progression of his hemianopia to complete as well as mild right lower extremity weakness; this latter finding had resolved by the next evaluation. He subsequently underwent 6 additional staged embolization procedures. During this course, he was intermittently reported to have a facial palsy; he also experienced access site (femoral) complications (bleeding) from at least 4 of these procedures. Onyx-18 was used for all procedures, except for the next to last procedure; on 4/28/02, Onyx was not administered because the physician felt it was necessary to embolize one of the feeders with Embospheres, a nonassigned embolic agent; at the last embolization, performed immediately pre-operatively, Onyx-18 was delivered to one of the feeders and Embospheres was administered to another of the feeding arteries. At the completion of the series of embolizations, the AVM had a 97% reduction. On 6/21/02, approximately 9 days after his last embolization, he underwent elective surgery. Post-op angiography documented complete resection of the AVM but there was marked attenuation of the left middle cerebral artery and its branches. A follow-up CT demonstrated a large MCA distribution infarction and the patient had a dense right hemiparesis. He remained intubated and receiving supportive care until 6/27/02 when the family requested he be extubated. The patient expired on 6/28/02. *The complication report fpr patient 08-005, states that "Large blood vessels remote from the AVM were found to be occluded on a post-surgical angiogram." Please describe what material caused the occlusion and provide copies of angiograms for panel review.*

In the Cordis study comparing n-BCA to PVA, 4 patient deaths occurred, 4%, and a total hemorrhagic complication rate of 13 to 29% was reported.

Patient Terminations

Patient 03-003 had the second embolization procedure done through both left and right femoral artery access; patient was randomized to Onyx. At the second embolization, the patient was crossed over to n-BCA. *Please clarify whether n-BCA and Onyx were used during the second embolization attempt on patient 03-003. Please discuss the finding on a small right superior cerebellar ischemic lesion found on the MRI, following embolization and state which agent had been used for this embolization. Please state why the patient was terminated and whether the patient had radiosurgery following the embolization.*

Patient 08-006 was randomized to n-BCA. The patient had a "procedural event," a pulmonary embolism. Onyx was used for the second embolization, but the delivery catheter could not reach the target and therefore the patient could not be treated. After the second embolization, the patient had radiosurgery.

Patient 08-009 was randomized to n-BCA; no embolization was done because microcatheter access was lost and was unable to recannulate. Therefore, the patient was a failure to treat and terminated.

Patient 10-003 was randomized to n-BCA. After the first embolization, the patient's insurance refused to pay for additional treatment of the AVM; therefore, the second embolization and surgical resection were not done and the patient was terminated from the study.

Patient 19-001 was randomized to n-BCA. The AVM involved the middle temporal lobe and the blood supply was from the branches of the middle cerebral artery. It was not possible to embolize the AVM because of high flow. *You state that the AVM in patient 19-001 involved the middle temporal lobe and the blood supply was from the branches of the middle cerebral artery. Therefore, it was not possible to embolize the AVM with n-BCA because of high flow. Please discuss whether this patient had any other embolization treatment, surgery, or radiosurgery.*

Patient 20-002 was randomized to n-BCA. For the second embolization, Berenstein liquid coils were used with n-BCA. This patient was lost to follow-up.

Patient 21-007 was randomized to n-BCA. The patient was terminated because the neurointerventionalist decided the feeding vessels were better treated with PVA as the primary embolic agent. *You state that patient 21-007, who was randomized to n-BCA, was terminated because the neurointerventionalist decided the feeding vessels were better treated with PVA as the primary embolic agent. Please discuss whether this patient had any other embolization treatment, surgery, or radiosurgery.*

Patient 21-008 was randomized to n-BCA. It is stated that the coils were used because the "anatomy defined during microcatheterization favored particulate embolization." One day postembolization, the patient suffered a small Subarachnoid and intraventricular hemorrhage; no neurologic changes were noted by the MD. *You state that coils were used because the "anatomy defined during microcatheterization favored particulate embolization" in patient 21-008 who was randomized to n-BCA. One day postembolization, the patient suffered a small Subarachnoid and intraventricular hemorrhage; no neurologic changes were noted by the MD. Please discuss whether this patient had any other embolization treatment, surgery, or radiosurgery.*

Patient 32-003 was randomized to Onyx, however, the n-BCA embolization CRF was completed. Berenstein liquid coils were used during the embolization procedure. The CRF stated that there was an inability to adequately position the ultraflow resulting in use of Spinnauer-elite and crossover to n-BCA. *You state that patient 32-003 was randomized to Onyx, however, the n-BCA embolization CRF was completed. Berenstein liquid coils were used during the embolization procedure. The CRF stated that there was an inability to adequately position the ultraflow resulting in use of Spinnauer-elite and crossover to n-BCA. Please discuss whether this patient had any other embolization treatment, surgery, or radiosurgery.*

Patient 34-001 was randomized to n-BCA but none was used because the physician could not advance the catheter distally. Post-surgery, the patient had severe left sided hemiparesis, meningitis, GI bleed, hydrocephalus which required a ventriculostomy, an intraventricular hemorrhage involving both lateral ventricles, third and fourth ventricles, acute respiratory failure, and a large hematoma in the right frontal lobe, temporal lobe, and right basal ganglia. *You state that patient 34-001 was randomized to n-BCA but none was used because the physician could not advance the catheter distally. Post-surgery, the patient had severe left sided hemiparesis, meningitis, GI bleed, hydrocephalus which required a ventriculostomy, an intraventricular hemorrhage involving both lateral ventricles, third and fourth ventricles, acute respiratory failure, and a large hematoma in the right frontal lobe, temporal lobe, and right basal ganglia. Please discuss whether this patient's medical condition returned to normal and whether he had any other embolization treatment, surgery, or radiosurgery.*

You provided CRFs for the following terminated patients, 10-003, 20-002, 21-007 and 34-001. However, these patients are not listed in the ITT Analysis Flowchart on page 3161 as terminations or lost to follow-up. Please explain this discrepancy and revise the table if necessary. Furthermore, CRFs were not provided for patients 8-004 and 2-001 whose films were not analyzable and patients 2-012, 6-007, 6-013, 8-007, and 8-012 who were treatment failures.

Device Malfunctions

The Flow Rider Plus catheter ruptured 10 cm from the top of the catheter on patient 20-003; there was Onyx leakage

with "untoward embolization" and no clinical sequelae. *Please discuss the "untoward embolization" that occurred when the Flow Rider Plus catheter ruptured on patient 20-003.*

This table includes a summary of all serious adverse events that occurred in patients and therefore, patients may be cited more than once. However, if a patient had a series of cascading events that were linked together, the primary leading serious adverse event is listed in the table. A total of 48 events were observed in 34 patients; the majority of the events were categorized as either an intracranial hemorrhage or a worsening of neurologic status.

Event	N-BCA n=54	Onyx n=46
Intracranial Hemorrhage	9	7
Stroke	0	2
Worsening Neuro Status	4	7
Persistent	3	5
Transient	1	2
Multi-Organ System Complications	1	0
Severe Bleeding/Low Hct requiring transfusion	1	0
Hydrocephalus	0	1
Respiratory Failure	1	1
Infection	2	1
Seizures	0	1
Fever	1	0
Catabolic State	1	0
Vessel Dissection	0	1
Limb Ischemia	1	0
Headache +/- Nausea and Vomiting	3	1
Medication Reaction	0	2
Total # SAEs	24	24
# Pts with SAE	15	19

Intracranial hemorrhage is a known risk of surgery for AVM resection.

Please provide the patient ID for each of the serious adverse events listed in the Serious Adverse Event – Non-Hierarchical on page 3177.

	# SAEs	
Spetzler-Martin Grade #Events (#Pts with Event)	N-BCA	Onyx
1	4 (3)	2 (1)
2	4 (3)	8 (7)
3	4 (4)	10 (7)
4	12 (5)	4 (4)
Total	24 (15)	24 (19)

A Spetzler-Martin Grade of 3 or 4 was associated with a higher number of events in both the n-BCA and Onyx groups than the patients presenting with a Spetzler-Martin Grade of 1 or 2.

Please provide the patient ID for each of the serious adverse events listed in the Serious Adverse Events by Spetzler-Martin Grade on page 3179 and state the serious adverse event associated with each patient.

Intracranial Hemorrhage and Persistent Worsening Neuro Status by Spetzler-Martin Grade

	# SAEs	
Spetzler-Martin Grade	N-BCA	Onyx
#Events (#Pts with Event)		
1	2 (2)	1 (1)
2	3 (3)	5 (5)
3	2 (2)	4 (3)
4	6 (5)	2 (2)
Total	13 (12)	12 (11)

Intracranial Hemorrhage by Spetzler-Martin Grade

	# SAEs	
Spetzler-Martin Grade	N-BCA	Onyx
#Events (#Pts with Event)		
1	2 (2)	0
2	2 (2)	2 (2)
3	0	4 (4)
4	5 (4)	1 (1)
Total	9 (8)	7 (7)

Please provide the patient ID for each of the serious adverse events listed in the Serious Adverse Events by Spetzler-Martin Grade on page 3179 and state the serious adverse event associated with each patient. In addition, provide the patient ID for each of the patients referred to in the Intracranial Hemorrhage and Persistent Worsening Neuro Status by Spetzler-Martin Grade and Intracranial Hemorrhage by Spetzler-Martin Grade on page 3180.

Event relationship attribution is separated into the following categories:

1. System related which includes any event caused by the micro catheter and/or embolic agent
2. Treatment related including any event associated with the embolization procedure including the guidewire or other ancillary devices
3. Surgery related
4. Disease related.

Event	n-BCA n=54	Onyx n=46	p-value
	System		
Stroke	0	1	
Vessel Dissection	0	1	
Worsening Neurological Status	1	2	
Intracranial Hemorrhage	1	0	
Total #Events	2	4	
Total #Pts with Events	2/54 (3.7%)	4/46 (8.7%)	0.41
	Treatment		
Headache +/- Nausea and Vomiting	0	1	
Intracranial Hemorrhage	2	2	
Limb Ischemia	1	0	
Medication Reaction	0	2	
Worsening Neurologic Status	1	2	
Total #Events	4	7	
Total #Pts with Events	3/54 (5.6%)	5/46 (10.9%)	0.46
	Surgery		
Infection	2	1	
Catabolic State	1	0	
Headache +/- Nausea and Vomiting	2	0	
Intracranial Hemorrhage	6	5	
Multi-Organ System Complications	1	0	
Respiratory Failure	1	0	
Severe Bleeding/Low HCT ReqTransfusion	1	0	
Stroke	0	1	
Worsening Neurological Status	2	3	
Fever	1	0	
Total #Events	17	10	
Total #Pts with Events	11/54 (20.4%)	10/46 (21.7%)	1.00
	Disease		
Seizures	0	1	
Headache +/- Nausea and Vomiting	1	0	
Hydrocephalus	0	1	
Respiratory Failure	0	1	
Total #Events	1	3	
Total #Pts with Events	1/54 (1.9%)	2/46 (4.4%)	0.60
Overall Total #Events	24	24	

There were 2 system related adverse events in the n-BCA group and 4 in the Onyx group; each of these events was associated with a specific patient. One event in each treatment group was considered to be associated with the embolic agent itself and the other events were considered to be associated with the micro catheter. One of the events in the n-BCA group, 05-001 was associated with either the micro catheter or the guidewire. All other events with known association to the guidewire are summarized in the treatment-related category. Patient 05-001 was noted to have an intracranial hemorrhage; this was documented on CT following the patient's third embolization procedure and required emergency surgery; it was felt that this perforation was related to either guidewire or delivery catheter manipulation. One patient in the n-BCA group, 38-002 and two patients in the Onyx group, 32-002, 20-003 experienced events categorized as worsening neurologic status. The patient in the n-BCA group experienced a severe deficit of right sided weakness that was associated with the embolic agent being administered to an

unintended vessel. One of the patients that had a worsening neurologic status in the Onyx group, 32-002, has vasospasm that caused the neurologic deficit; the vasospasm was associated with difficulty removing the Onyx delivery catheter but the neurologic deficit was transient and resolved completely prior to patient discharge. The second patient, 20-003, that had a worsening neurologic status was considered to be associated with difficulties the physician had with the Onyx delivery catheter, the FlowRider Plus; the catheter malfunctioned and ruptured during Onyx administration; the micro catheter was withdrawn from the market and replaced with the UltraFlow catheter; the worsening neurological status that was associated with this malfunction was transient and completely resolved over the subsequent several days. One patient in the Onyx group, 06-007 had a vessel dissection in the vertebral artery that was considered to be associated with either the micro catheter or the guidewire; the dissection occurred during the first embolization but was not identified until the patient presented for the scheduled second embolization treatment; no embolization was performed at that time. The patient was initially followed clinically with the addition of antiplatelet agents. During a subsequent procedure, the vessel dissection was treated with percutaneous balloon angioplasty and stent placement. Approximately 1 month later the treated vessel was widely patent and embolization was performed with no complications or sequelae; another embolization was performed with no sequelae. The stroke that occurred in the Onyx patient, 06-004, was associated with the embolic material being deliverd to a non-target vessel.

Events related to the embolic procedure itself or adjunctive devices during the procedure have been categorized as treatment related. There were 4 events in the n-BCA group and 7 in the Onyx group; these events occurred in 3 of the 54 total n-BCA patients and 5 of the 46 Onyx patients. In the n-BCA group, one ICH was determined to be associated with a guidewire perforation; also one worsening neurologic status was caused by contrast extravasation that occurred after a guidewire perforation. None of the treatment related AEs in the Onyx group were associated with any ancillary devices.

The majority of SAEs were related to the surgical resection of the AVM. 17 of the 24 total events in the n-BCA, 71%, group were surgery related; these 17 events occurred in 11 patients resulting in a surgery related SAE rate of 20% in the n-BCA group. 10 of the 24 events in the Onyx group were surgery related; the 10 events in 10 patients resulted in a surgery related SAE rate of 22% in the Onyx group.

One SAE in the n-BCA group and 3 in the Onyx group were considered to be caused by the clinical disease state. One patient experienced respiratory failure but this patient was enrolled in the trial in a comatose state and the respiratory failure was considered to be more associated with the poor clinical state than any of the procedures that the patient had for treatment of the AVM.
Please provide the patient ID and a description of each of the serious adverse events listed in the Serious Adverse Events by Relationship on page 3181.

Predictors of Serious Adverse Events

Characteristic	No SAE n=66	SAE n=384	p-value
Gender (%male)	52%	38%	P=0.30
AVM Location (%right/left)	95%	100%	P=0.55
Eloquent Part of Brain	44%	56%	P=0.30
Spetzler-Martin Grade (% 3 or 4)			P=0.20
Venous Drainage (% deep)	40%	35%	P=0.83
Presence of Bleed	29%	41%	P=0.26
Glasgow Coma Scale (%<15)	6%	15%	P=0.26
Corelab-ITT Success	93%	85%	P=0.27
Corelab-Protocol Success	93%	90%	P=0.70
Age (mean±sd, years)	37±17	39±16	P=0.54
BMI	26±6	26±5	P=0.93
SBP (mean±sd, mmHg)	126±13	121±19	P=0.16
DBP (mean±sd, mmHg)	71±11	70±11	P=0.56
AVM Size (median, mm^3)	8.1	15.5	P=0.04
# Embolization Procedures (mean±sd)	1.6±1.0	2.1±1.3	P=0.02
#Surgeries (mean±sd)	1.0±0.1	1.3±0.7	P=0.06
Length of Surgery (median, min)	328	505	P=0.0004
Blood Loss (median, ccs)	497	994	P=0.003
Randomization Group (% Onyx)	41%	56%	P=0.20

Predictors of SAEs included AVM size, number of embolization procedures, length of surgery, and blood loss. The significant parameters from the univariate anslysis were entered into a multivariate regression model to determine the predictors of SAEs. By multivariate analysis, surgical blood loss was the only predictor of SAE, p=0.03.

Non-serious AEs include anything categorized as minor or moderate as defined in the protocol. This summary table represents a compilation of all events that occurred in the patients and thus patients may be cited more than once. However, if a patient had a series of cascading events that were linked together, only the primary leading AE is listed.

Non-Serious AEs

Event by Relationship	N-BCA n=54	Onyx n=46
	System Related	
Total	0	0
	Treatment Related	
Access Site Bleeding	0	5
Headache +/- Nausea and Vomiting	20	21
Medication Reaction	1	1
Pt Discomfort	4	7
Worsening Neurologic Status	13	9
Total	38	43
	Surgery Related	
Cardiac Arrhythmia	0	1
Medication Reaction	1	0
Laboratory/Imaging Abnormalities	1	1
Intracranial Hemorrhage	1	1
Infection	1	2
Seizures	1	0
Fever	1	3
Severe Bleeding/Low HCT Req Transfusion	1	0
Headache +/- Nausea and Vomiting	7	9
Tongue Swelling	0	1
Worsening Neurologic Status	8	6
Pt Discomfort	5	7
Total	27	31
	Disease Related	
Psychotic Episode	0	1
Worsening Neurologic Status	2	2
Pt Discomfort	1	0
Laboratory/Imaging Abnormalities	1	0
Infection	2	2
Hydrocephalus	1	1
Headache +/- Nausea and Vomiting	2	1
Thrombocytopenia	1	0
Total	10	7
	Other Related	
Medication Reaction	1	1
Pt Discomfort	1	1
Total	2	2
	Unknown Related	
Worsening Neurologic Status	2	0
Pt Discomfort	0	2
Total	2	2
Total #Non-Serious AEs	79	85
Total # Pts with Non-Serious AEs	50	41

Similar to the SAEs, intracranial hemorrhage and worsening neurologic status comprised the majority of events. One patient in the n-BCA group had a worsening of neurological status that was caused by contrast extravasation; the event occurred following a guidewire perforation.

Although the patient based rate of SAEs is higher for the Onyx group, the total number of SAEs is equal in both groups and no differences were found to be statistically significantly different.
Please provide the patient ID and a description of each of the non Serious adverse events listed in the Non Serious Adverse Events on page 3187.

Adverse events not observed during the study include AVM rupture and pulmonary embolism.

Pts with serious AE	N-BCA N=54	Onyx N=46	p-value
Serious AE	27.8% (15)	41.3% (19)	0.20
System-related SAE	3.7% (2)	8.7% (4)	0.41
Treatment-related SAE	5.6% (3)	10.9% (5)	0.46
Surgery-related SAE	20.4% (11)	21.7% (10)	1.00
Disease-related SAE	1.9% (1)	4.3% (2)	0.60

Labelling

Cautions

- Performing embolization to occlude blood vessels is a high risk procedure. This device should only be used by physicians with neurointerventional training and a thorough knowledge of the pathology to be treated, angiographic techniques, and super-selective embolization.
- Failure to wait a few seconds to retrieve the micro catheter after Onyx injection may result in fragmentation of Onyx into non-target vessels.
- Difficult catheter removal or catheter entrapment may be caused by any of the following:
  - Angioarchitecture: very distal AVM fed by afferent, lengthened, and tortuous pedicles
  - Vasospasm
  - Reflux
- Should catheter removal become difficult, the following will assist in catheter retrieval:
  - Carefully pull the catheter to assess any resistance to removal.
  - If resistance is felt, remove any "slack" in the catheter.
  - Gently apply traction to the catheter (approximately 3-4 cm of stretch to the catheter).
  - Hold this traction for a few seconds and release. Assess traction on vasculature to minimize risk of hemorrhage.
  - This process can be repeated intermittently until catheter is retrieved.
- For entrapped catheters:
  - Under some difficult clinical situations, rather than risk rupturing the malformation and consequent hemorrhagic complications by applying too much traction on an entrapped catheter, it may be safer to leave the micro catheter in the vascular system.
  - This is accomplished by stretching the catheter and cutting the shaft near the entry point of vascular access allowing the catheter to remain in the artery.
  - If the catheter breaks during removal, distal migration or coiling of the catheter may occur. Same day surgical resection should be considered to minimize the risk of thrombus.

Contraindications

- Not for use with premature infants (<1,500 g) or individuals with significant liver function impairement.

Warnings

- Inspect product packaging prior to use. Do not use if sterile barrier is open or damaged.
- Verify that adequate sedation is used throughout the embolization procedure. Insufficient sedation may result in patient discomfort or movement. Patient movement during embolic agent injection may result in embolization of an unintended vessel.

  NOTE: Adjunctive coil use should be considered if angiography shows that venous drainage of the AVM appears almost simultaneously with arterial opacification. Based on results from in vitro and in vivo testing, coil placement prior to Onyx injection should be considered for feeding pedicles with AV fistulae

having flow rates exceeding 200 ml/min and vessel diameters of 3 mm or greater.

- Failure to continuously mix Onyx for the required time may result in inadequate suspension of the tantalum, resulting in inadequate fluoroscopic visualization during delivery.
- Use only MTI micro catheters. Other micro catheters may not be compatible with DMSO and their use can result in thromboembolic events due to catheter degredation.
- Use only the MTI 1 ml syringe to inject DMSO and Onyx. Other syringes may not be compatible with DMSO.
- Premature solidification of Onyx may occur if micro catheter luer contacts saline, blood, or contrast of any amount.
- Inject Onyx immediately after mixing. If Onyx injection is delayed, tantalum settling can occur within the syringe resulting in poor visualization of Onyx during injection.
- Do not exceed 0.3 ml/min injection rate. Animal studies have shown that rapid injection of DMSO into the vasculature may lead to vasospasm and/or angionecrosis.
- Only use thumb pressure to inject Onyx. Using palm of hand to advance plunger may result in catheter rupture due to overpressurization in the event of catheter occlusion.
- Adequate fluoroscopic visualization must be maintained during Onyx delivery or non-target vessel embolization may result. If visualization is lost at any time during the embolization procedure, HALT Onyx delivery until adequate visualization is re-established.
- Do not allow more than 1 cm of Onyx to reflux back over catheter tip. Excessive Onyx reflux may result in difficult catheter removal.
- After using a micro catheter with Onyx, do not attempt to clear or inject any material through it. Such attempts may lead to embolus or embolization of an unintended area.
- STOP injection if Onyx is not visualized exiting catheter tip. If the catheter becomes occluded, over-pressurization can occur. During Onyx injection, continuously verify than Onyx is exiting the catheter tip. Testing has shown that over-pressurization and rupture can occur if 0.05 ml of Onyx is injected and is not visualized exiting the catheter tip.
- STOP injection if increased resistance to Onyx injection is observed. If increased resistance occurs, determine the cause (e.g. Onyx occlusion in catheter lumen) and replace the catheter. Do not attempt to clear or overcome resistance by applying increased injection pressure, as use of excessive pressure may result in catheter rupture and embolization of unintended areas.
- DO NOT interrupt Onyx injection for longer than two minutes prior to re-injection. Solidification of Onyx may occur at the catheter tip resulting in catheter occlusion, and use of excessive pressure to clear the catheter may result in catheter rupture.

Pathological Assessment of Human AVMs

Studies were conducted to assess the effects of brain and neurovascular tissue exposure to Onyx and n-BCA materials. For one retrospective masked study, CT, MRI, and flat film skull X-rays obtained from patients in a sponsor-investigator IDE, with AVMs treated with Onyx were reviewed and compared to a cohort of patients with n-BCA treated AVMs. A total of 54 patients were studied in the Onyx group and 19 in the n-BCA group, for a total of 73 patients. The analysis spanned a post-embolization period of up to 50 months. An independent blinded central reader reviewed both pre- and post-embolization CT and MRI films to determine whether any direct neurotoxicity due to Onyx or n-BCA could be detected. Films were evaluated for the presence or absence of gliosis, encephalomalacia, edema, leptomeningeal , or parenchymal enhancement and hemorrhage. These parameters were predefined based on specific imaging characteristics. Analysis of the films revealed no immediate or delayed imaging abnormalities that could be attributed to the presence of the embolic material.

In a second study, histopathological evaluations of 7 human brain AVMs were performed following embolization with Onyx and surgical resection. BAVM sizes ranged from 2.30 to 93.65 cm^3, mean size 35 cm^3. Prior to surgery, one patient received a single embolization treatment, 2 patients received 2 treatments, 1 patient received 3 treatments, and 3 received 4 treatments. All AVMs had pre-surgical embolization periods of at least 3 months, with 4 of 7 embolized more than 6 months, and 3 of 7 at approximately 12 months up to 19 months. >90% of the Onyx material was within blood vessels of 500µm or greater. The remaining 10% of material was seen in vessels 100-500

µm. There was no reported evidence of fragmentation or distal migration of material; there were no reported ischemic or hemorrhagic complications resulting from untoward migration or abrupt occlusion of an AVM nidus.

Pt	#Embolic Proc	Path Eval Onyx Implanted Period	DMSO Vol (ml)	Onyx Vol (ml)	Initial AVM Size (cm^3)	Final AVM Size (cm^3)	% Size Red
KACN	4	1 wk, 6,7,19 mo	1.12	2.65	93.7	13.6	85
LRR	3	4,8 mo	1.02	1.40	2.3	0.6	77
AZB	3	6,11,12 mo	2.05	1.35	21.8	2.0	91
SGC	4	1 wk,10,12,13 mo	1.64	0.71	67.6	25.0	63
LMC	2	1,2,3 mo	1.20	0.69	25.7	0.4	98
PW	4	1,2,3 mo	1.90	4.08	14.4	2.6	82
LMRM	1	11 mo	0.60	0.60	20.2	3.2	84

The histopathology reports show no indication of vascular necrosis, rupture, or extravasation of the Onyx material. Numerous vessels were noted with disruption of the internal elastic lamina, but there did not appear to be any serious adverse effect on the vessel wall. The finding of intramural accumulations of neutrophils at multiple sites in the vessels or SGC was the most adverse morphologic change observed. The finding was inconsistent with other specimens in the study and attributed to an unrelated infection or presence of a strongly birefringent foreign material other than Onyx found in the vessels.

Summary of Dural Fistulae Patients

Pt	Tx	Age	Gender	SBP	DBP
02-008	Onyx	64	Female	135	46
05-005	N-BCA	34	Male	100	76
08-008	Onyx	53	Male	144	92
08-010	Onyx	57	Male	106	66
08-014	Onyx	66	Male	170	95
38-001	Onyx	66	Male	100	58
Mean±SD		58±14		126±28.6	72.2±19.3

3 patients were enrolled with a presenting acute intracranial hemorrhage, 2 patients with neurological deficit, and 1 with neurological symptoms. 3 patients were unassessable by the core lab; 2 were failures and 1, 08-014, was a success. 4 patients underwent surgical resection; there are no plans for surgery for the other 2 patients. Pneumonia developed in patient 08-008 that was secondary to his inability to protect his airway due to the development of worsening neurologic status; the patient was hospitalized, treated with antibiotics and steps were taken to prevent aspiration.

Adverse Events

	Relationship			
AE	Disease	Treatment	Surgery	Total
Headache +/-Nausea and Vomiting		1		1
Infection		1		1
Medication Reaction		1		1
Pt. Discomfort			1	1
Seizures	2			2
Worsening Neurologic Status	1	2	2	3

6 of the 9 events resolved by the end of the follow-up interval. One event was ongoing and the remainder had recovered but with some residual deficit.

Please provide the patient ID and a description of each of the adverse events listed in the Dural Fistulae Adverse Events table on page 3705.

Patients who did not have a complete surgical resection

9 patients did not undergo complete surgical resection of the AVM and therefore are being followed at 3 and 12 months. 3 patients had partial resection of their AVM and 6 had no attempt at resection. 5 of the 9 patients were determined to be successes by the core lab, 3 were failures, and 1 was not assessable. 4 of the patients are scheduled

to undergo some type of radiosurgery.

Pt	Tx	Date Last Embo or Sx	Result	Barthel			NIH			Glasgow		
				Last Tx	3 mos	12 mos	Last Tx	3 mos	12 mos	Last Tx	3 mos	12 mos
10-005	N-BCA	7/8/02	Success	90	100	N/A	0	0	N/A	0	0	N/A
29-002	Onyx	10/15/01	Success	25	85	100	0	0	0	1	1	0
29-006	Onyx	11/5/02	Success	35	100	N/A	0	0	N/A	0	2	N/A
08-004	N-BCA	1/29/02	Missing	100		100	0		0	0		0
08-006	N-BCA	1/8/02	Failure	100			0			15		
08-012	N-BCA	7/23/02	Failure	100		N/A	0		N/A	15		N/A
20-003	Onyx	7/8/02	Success	45		N/A	7		N/A	15		N/A
34-001	N-BCA	12/3/02	Success	*		N/A	*		N/A	*		N/A
38-008	N-BCA	12/3/02	Success	100	N/A	N/A	0	N/A	N/A	15	N/A	N/A

*Primary technical failure, no post treatment information provided

N/A= Not due

No serious AEs occurred following their last treatment, surgery or embolization. 29-006 had a reduction in functional status as demonstrated by the increase in Glasgow score due to multiple systemic complaints. 08-006 had generalized pain that was reported at the time of hospital visit for scheduled radiosurgery.

Summary of Protocol Deviations

Deviation	#Occurrences
Dural Fistula Pts	6
Neuro Assessment not Performed or Performed Outside Specified Window	85
Core Lab Issues	32
-Different Views Pre and Post Proc	
-No Dimes on Films	
-Missing Films	
-Pre Images Contain Embolic Material	
Use of Outdated MRI/CTcrf	29
Sequential Embolization Performed Beyond the Protocol Recommendation of 4 Weeks	26
CRF Not Filled Out or Items on CRF Missing	11
Patient did not Go to Surgery	7
Not Blinded	6
Rate of Onyx Release Exceeded Recommended Guidelines	5
EBL Not Assessable/Not Documented Properly	4
Use of Embospheres with Onyx	2
Opened Randomization Envelope Prior to Full Patient Assessment	2
CT Not Done	2
Crossover to n-BCA	2
LTFU	2
Other	4

The 85 neurologic assessments represent approximately 12% of the expected neurologic exams to be performed. Neurologic outcome was available in almost all cases post final embolization and post surgery. Although the core lab was listed as having 32 protocol deviations, these angiographic assessment deviations only resulted in a few cases were the efficacy endpoint was not able to be assessed, a total of 4 films were missing or unassessible.

In the Protocol Deviation Summary on page 3722, please specify the number of protocol deviations associated with each of the 32 core lab issues. In addition, please discuss the four "other" protocol deviation.

Patient Demographics by Group (All Patients, n=108)

Demographics	N-BC n=57	Onyx N=51
Age (yrs)		
Mean +/- SD (n)	35.1 $\pm$ 14.2 (57)	42.5 $\pm$ 17.0 (51)
Median (range)	35.0 (10.0-66.0)	44.0 (7.0-73.0)
Gender		
Male	49.1% (28/57)	45.1% (23/51)
Female	50.9% (29/57)	54.9% (28/51)
BMI		
Mean +/- SD (n)	24.4 $\pm$ 4.5 (54)	28.1 $\pm$ 6.3 (41)
Median (range)	23.7 (15.1-37.2)	27.4 (16.7-45.0)
Systolic Blood Pressure (mmHg)		
Mean +/- SD (n)	123 $\pm$ 14 (57)	127 $\pm$ 17 (51)
Median (range)	120 (80-171)	127 (98-170)
Diastolic Blood Pressure (mmHg)		
Mean +/- SD (n)	71 $\pm$ 10 (57)	71 $\pm$ 13 (51)
Median (range)	70 (50-90)	70 (46-98)

Medical History by Treatment Group (All Patients, n=108)

Medical History	N-BCA	Onyx
n=108	n=57	n=51
CAD	1.8% (1/57)	5.9% (3/51)
HTN	19.3% (11/57)	21.6% (11/51)
Diabetes	5.3% (3/57)	9.8% (5/51)
Neuro History		
Seizure	21.1% (12/57)	9.8% (5/51)
Stroke	0.0% (0/57)	2.0% (1/51)
Aneursym	8.8% (5/57)	0.0% (0/51)
Other AVM	3.5% (2/57)	2.0% (1/51)
Neuro Interventions		
Surgery (Clipping)	5.3% (3/57)	0.0% (0/51)

Please provide the number and percentage of patients in each group who had an intracranial hemorrhage > 1year.

Hierarchical Presenting Symptoms by Treatment Group (All Patients, n=108)

Hierarchical Presenting Symptoms	N-BCA	Onyx
n=108	n=57	n=51
Acute Bleed (<30 days)	14.0% (8/57)	19.6% (10/51)
Remote Bleed (>30 days<1 year)	17.5% (10/57)	17.6% (9/51)
Neurologic Deficit	52.6% (30/57)	37.3% (19/51)
Neurologic Symptoms	14.0% (8/57)	19.6% (10/51)
None	1.8% (1/57)	5.9% (3/51)

Baseline Neurologic Assessments by Treatment Group (All Patients, n=108

	N-BCA	Onyx
Pretreatment Assessment	n=57	n=51
Glasgow Coma Score		
0-6	3.6% (2/56)	3.9% (2/51)
7-14	3.6% (2/56)	7.8% (4/51)
>14	92.9% (52/56)	88.2% (45/51)
Barthel Index (Total Score)		
0-25	3.6% (2/55)	9.8% (5/51)
26-75	1.8% (1/55)	5.9% (3/51)
76-100	94.5% (52/55)	84.3% (43/51)
NIH Stroke Scale (Total Score)		
0	75.5% (41/54)	56.9% (29/51)
1-4	18.5% (10/54)	29.4% (15/51)
5-10	5.6% (3/53)	5.9% (3/51)
>10	0.0% (0/54)	7.8% (4/51)

Pretreatment Assessment (All Patients, n=108)

Pretreatment Assessment n=111 AVMs in 108 pts	N-BCA n=57 AVMs	Onyx n=54 AVMs
AVM Location		
Right	56.1% (32/57)	55.6% (30/54)
Left	40.4% (23/57)	35.2% (19/54)
Midline	3.5% (2/57)	9.3% (5/54)
AVM in eloquent area of brain	47.4% (27/57)	48.1% (26/54)
Venous Drainage		
Deep	8.8% (5/57)	18.5% (10/53)
Superficial	61.4% (35/57)	61.1% (33/53)
Both	29.8% (17/57)	18.5% (10/53)
AVM Size (Core Lab, mm^3)		
Mean±SD	16.0±20.0	26.3±44.0
Median	7.9	13.4
Range	0.1-94.9	0.2-290.5

In the Pretreatment Assessment table of all patients, please provide the Spetzler-Martin Grade for both groups.

ITT Analysis (All Patients, n=108)

	Total Pts=n	N-BCA=n	Onyx=n
Randomized	108	57	51
Late Screen Failures	2	2 (18-003, 21-009)	
Enrolled Pts	106	55	51
Protocol violations (Dural Fistulas)	6	1 (5-005)	5 (2-008, 8-001, 8-010, 8-014, 38-001)
ITT Analysis n=100 Ever Attempted Tx	100	54 55	46 50
Films not Analyzable	7	3 (21-008, 8-004, 5-005))	4 (32-003, 2-001, 8-008, 8-010)
Pts Ongoing	3	1 (38-004)	2 (38-006, 3-003)
Total Accessible	96	51 Success n=43 Failure n=8 Success Rate=84% (43/51) (Failures by CL: 6-003, 19-001, 34-001, 2-012, 8-012, 8-007) (Procedure Failure: 8-006, 8-009)	45 Success n=42 Failure n=3 Success Rate=93% (42/45) (Failures by CL: 6-007,2-008,38-001)

Please explain in the ITT Analysis of all patients on page 3710, how you jump from 100 patients that ever attempted treatment (n-BCA=54, Onyx=51) to n-BCA, n=55 and Onyx, n=50 and how in the n-BCA group, there are 51 patients that are totally accessible if 3 had films that were not analyzable and 1 is ongoing and in the Onyx group there are 45 patients if 4 had films that were not analyzable and 2 patients were ongoing. Please explain the difference between patients who were failures by core lab and those who were procedure failures.

Per-Protocol Analysis (All Patients, n=108)

	Total Pts=n	N-BCA=n	Onyx=n
Randomized	108	57	51
Late Screen Failures	2	2 (18-003, 21-009)	
Enrolled Pts	106	55	51
Protocol violations (Dural Fistulas)	6	1 (5-005)	5 (2-008, 8-001, 8-010, 8-014, 38-001)
ITT Analysis n=100 Ever Attempted Tx	100	54	46
Technical Failures (during 1st attempt): no embolization with intended device	4	3 (8-009, 19-001, 34-001)	1 (32-003)
		52	50
Films not Analyzable	5	2 (8-004, 5-005))	3 (2-001, 8-008, 8-010)
Pts Ongoing	3	1 (38-004)	1 (38-006)
Total Accessible	96	49 Success n=42 Failure n=7 Success Rate=86% (42/49) (Failures by CL: 6-003, 2-012, 8-012, 8-007) (Procedure Failure abandon treatment: 8-006, 21-007, 21-008)	46 Success n=42 Failure n=2 Success Rate=95% (42/46) (Failures by CL: 6-007,2-008,38-001) (Procedure Failure: 3-003)

From page 3711, please explain how you calculate that there are 52 patients in the n-BCA group and 50 in the Onyx group when there were 54 in the n-BCA and 46 in the Onyx group in the ITT analysis, that ever attempted treatment, and 3 in the n-BCA group and 1 in the Onyx group that were technical failures. Also please explain how you determined that there were 2 failures in the Total Accessible Onyx group when there were 3 patient failures assessed by the core lab and 1 procedure failure.

Primary Endpoint Summary

	N-BCA n=54	Onyx N=46
Core Lab Angiographic Success		
ITT Analysis	84% (43/51)	93% (42/45)
Per Protocol Analysis	86% (42/49)	91% (42/46)

Please explain why you used 54 patients in the n-BCA group and 46 in the Onyx group for the primary endpoint on page 3712 and 45 in the Onyx denominator for the ITT analysis.

Safety Endpoint Summary

Safety (Pt Based) %Patients (Pts with SEA/total sample)	N-BCA N=55	Onyx N=51
Serious AE	27.3% (15/55)	39.2% (20/51)
System-related SAE	3.6% (2/55)	7.8% (4/51)
Treatment-related SAE	5.4% (3/55)	9.8% (5/51)
Surgery-related SAE	20.0% (11/55)	19.6% (10/51)
Disease-related SAE	1.8% (1/55)	3.9% (2/51)

Serious AEs Hierarchical Event	n-BCA	Onyx

	n=55	N=51
Death	0 (0%)	2 (3.9%)
Intracranial Hemorrhage	8 (14.5%)	6 (11.8%)
Stroke	0 (0%)	1 (2%)
Infection	0 (0%)	1 (2%)
Worsening Neuro Status	5 (9.1%)	7 (13.7%)
Hydrocephalus	0 (0%)	2 (3.9%)
Seizures	0 (0%)	1 (2%)
Headache +/- nausea and vomiting	2 (3.6%)	0 (0%)
Total patients	15	20

Serious AEs not Hierarchical

Event	N-BCA n=55	Onyx n=51
Intracranial Hemorrhage	9	7
Stroke	0	2
Worsening Neuro Status	4	7
Persistent	3	5
Transient	1	2
Multi-Organ System Complications	1	0
Severe Bleeding/Low Hct requiring transfusion	1	0
Hydrocephalus	0	1
Respiratory Failure	1	1
Infection	2	1
Seizures	0	1
Fever	1	0
Catabolic State	1	0
Vessel Dissection	0	1
Limb Ischemia	1	0
Headache +/- Nausea and Vomiting	3	1
Medication Reaction	0	2
Total # SAEs	24	24

Please state the total number of patients with non-Hierarchical SAEs for the Serious Adverse Events – Non-Hierarchical table on page 3714.

Serious AEs by Relationship

Event	n-BCA n=55	Onyx n=51
System		
Stroke	0	1
Vessel Dissection	0	1
Worsening Neurological Status	1	2
Intracranial Hemorrhage	1	0
Total #Events	2	4
Total #Pts with Events	2/55 (3.6%)	4/51 (7.8%)
Treatment		
Headache +/- Nausea and Vomiting	0	1
Intracranial Hemorrhage	2	2
Limb Ischemia	1	0
Medication Reaction	0	2
Worsening Neurologic Status	1	2
Total #Events	4	7
Total #Pts with Events	3/55 (5.4%)	5/51 (9.8%)
Surgery		
Infection	2	1
Catabolic State	1	0
Headache +/- Nausea and Vomiting	2	0
Intracranial Hemorrhage	6	5
Multi-Organ System Complications	1	0
Respiratory Failure	1	0
Severe Bleeding/Low HCT ReqTransfusion	1	0
Stroke	0	1
Worsening Neurological Status	2	3
Fever	1	0
Total #Events	17	10
Total #Pts with Events	11/55 (20.0%)	10/51 (19.6%)
Disease		
Seizures	0	1
Headache +/- Nausea and Vomiting	1	0
Hydrocephalus	0	1
Respiratory Failure	0	1
Total #Events	1	3
Total #Pts with Events	1/55 (1.8%)	2/51 (3.9%)
Overall Total #Events	24	24

Please provide the patient ID and a description of each of the sSerious adverse events listed in the Serious Adverse Events by Relationship on page 3715.

Non Serious AEs

Event by Relationship	N-BCA n=55	Onyx N=51
	System Related	
Total	0	0
	Treatment Related	
Access Site Bleeding	0	5
Headache +/- Nausea and Vomiting	21	21
Infection	0	1
Medication Reaction	1	1
Pt Discomfort	4	7
Worsening Neurologic Status	13	11
Total	39	46
	Surgery Related	
Cardiac Arrhythmia	0	1
Medication Reaction	1	0
Laboratory/Imaging Abnormalities	1	1
Intracranial Hemorrhage	1	1
Infection	1	2
Seizures	1	0
Fever	1	3
Severe Bleeding/Low HCT Req Transfusion	1	0
Headache +/- Nausea and Vomiting	7	9
Tongue Swelling	0	1
Worsening Neurologic Status	8	6
Pt Discomfort	6	7
Total	28	31
	Disease Related	
Psychotic Episode	0	1
Worsening Neurologic Status	2	3
Pt Discomfort	1	0
Laboratory/Imaging Abnormalities	1	0
Infection	2	2
Hydrocephalus	1	1
Headache +/- Nausea and Vomiting	2	1
Thrombocytopenia	1	0
Total	10	7
	Other Related	
Medication Reaction	1	1
Pt Discomfort	1	1
Total	2	2
	Unknown Related	
Worsening Neurologic Status	2	0
Pt Discomfort	0	2
Total	2	2
Total #Non-Serious AEs	81	91
Total # Pts with Non-Serious AEs	51	46

Please provide the patient ID and a description of each of the non serious adverse events listed in the Non Serious Adverse Events on page 3716.

Technical/Procedural Events Summary

	N-BCA n=55	Onyx n=51
Technical Events (# of events)	11	18
Procedural Events (# of events)	12	3
Total Technical/Procedural Events (# of events)	23	21
Total Patients with Technical/Procedural Events (# of patients/% of patients)	31% (17/55)	27% (14/51)

Patient Follow-up Results

During the course of the trial, 9 patients did not undergo complete surgical resection of the AVM and are thus being followed at 3 and 12 months after the final embolization procedure or surgical attempt; 3 patients had partial resection of their AVM and 6 patients had no resection attempt. 5 of the 9 patients have been determined by the core lab to be successful embolization procedures and 3 patients have failed embolization procedures; the remaining patient's angiogram, 08-004, was not assessable by the core lab. During the follow-up interval, 4 patients underwent or are scheduled to undergo some type of radiosurgery.

No follow-up neurologic scale information is available on 5 patients.

Pt ID	Tx	Date last Embo or Sx	Outcome	Barthel			NIH			Glasgow		
				Last Tx	3 mos	12 mos	Last Tx	3 mos	12 mos	Last Tx	3 mos	12 mos
10-005	N-BCA	7/8/02	Success	90	100	N/A	0	0	N/A	0	0	N/A
29-002	Onyx	10/15/01	Success	25	85	100	0	0	0	1	1	0
29-006	Onyx	11/5/02	Success	35	100	N/A	0	0	N/A	0	2	N/A
08-004	N-BCA	1/29/02	Missing	100		100	0		0	0		0
08-006	N-BCA	1/8/02	Failure	100			0			15		
08-012	N-BCA	7/23/02	Failure	100		N/A	0		N/A	15		N/A
20-003	Onyx	7/8/02	Success	45		N/A	7		N/A	15		N/A
34-001	N-BCA	7/15/02	Failure	*		N/A	*		N/A	*		N/A
38-008	N-BCA	12/3/02	Success	100	N/A	N/A	0	N/A	N/A	15	N/A	N/A

*Primary technical failure, no post-treatment information provided
N/A=Not due

Only 2 patients, 08-006 and 29-006 had AEs during the follow-up period; no serious AEs occurred following their last treatment, surgery or embolization, episode. One patient, 29-006, had a reduction in their functional status as demonstrated by the increase in Glasgow score, from 0 to 2, due to multiple systemic complaints. The other patient, 08-006, had generalized pain that was reported at the time of the hospital visit for scheduled radiosurgery; the patient underwent radiosurgery without complication and the symptoms resolved spontaneously.